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30 June 2004

Shire

Gary Buehler
Division Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2
7500 Standish Place
Rockville, MD 20855

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| **Type of Submission:** | **Controlled Correspondence / Request for Comment and Dialogue** |
| **Re:** | **NDA No. 20-333, Division of Gastroenterology and Coagulation Drug Products** |
| **Product Name:** | **AGRYLIN® (anagrelide hydrochloride)** |

Dear Dr. Buehler:

With regard to the drug product Agrylin® (NDA 20-333), in accordance with the Office of Generic Drugs' (OGD) guidance on "controlled correspondence", Shire Pharmaceutical Development (Shire) is submitting a request for comment and dialogue with regard to monitoring of active metabolites in clinical bioequivalence studies. We are seeking OGD's guidance on the following question:

1. Does OGD agree that the active metabolite of anagrelide hydrochloride should be monitored in clinical bioequivalence studies?

Since the approval of Agrylin® in March 1997 by the FDA, Shire has progressed the development and approval of anagrelide in other international markets and this has resulted in further investigation and identification of the metabolites of anagrelide. The recent information on the role of the identified active metabolite, 3-hydroxy anagrelide, has been submitted to the FDA (Division of Gastroenterology and Coagulation Drug Products) as NDA supplements dated 12 March 2004 and 17 June 2004 to NDA 20-333 which included proposals to revise the product labeling.

For your information, a copy of the cover letter from the 12 March 2004 NDA supplement, and a full copy of the 17 June 2004 NDA supplement is included in this present "controlled correspondence" submission. The enclosed copy of the 17 June 2004 NDA supplement contains nonclinical and clinical pharmacokinetic data relevant to the active metabolite. It is Shire's opinion that the information presented and points raised in this letter and the supporting documents should be taken into consideration during the review of any pending anagrelide containing drug product ANDA submissions. We respectfully ask you to consider

a requirement for the measurement of the active metabolite of anagrelide in any clinical bioequivalence study.

As you are aware, the pediatric exclusivity period for Agrylin® expires on 11 September 2004, therefore, we look forward to the opportunity to discuss this issue with representatives of the OGD at your earliest convenience.

This "controlled correspondence" request is based on the following rationale:

- Recent nonclinical pharmacology and clinical pharmacokinetic studies have shown that the major metabolite of anagrelide, 3-hydroxy anagrelide, is considered to be responsible for most of the therapeutic platelet lowering activity and virtually all of the cardiovascular side effects associated with Agrylin®. Generation of this information was only possible following the successful chemical synthesis of 3-hydroxy anagrelide enabling the pharmacology and clinical pharmacokinetics of this metabolite to be examined.

- Clinical data (Shire study SPD422-202) indicate that the total plasma exposure (AUC, area under the plasma concentration-time curve) to this metabolite, 3-hydroxy anagrelide, in the target patient population exceeds that to anagrelide by 2.3:1. Note: the exposure to the metabolite is different in healthy volunteers.

- There is evidence that 3-hydroxy anagrelide is extensively (>50%) formed by first pass metabolism by CYP1A2 and that various extrinsic as well as intrinsic factors can significantly affect the amount of this active metabolite produced in vivo.

- A food interaction study (Shire study SPD422-109) suggests that the parent drug, anagrelide, may not necessarily act as a surrogate for the pharmacokinetic behaviour of the active metabolite 3-hydroxy anagrelide. While food significantly increased the AUC for anagrelide, it had no effect on the extent of exposure to the active metabolite. Furthermore food depressed the $C_{max}$ for the anagrelide twice as much as that of the active metabolite.

It is the opinion of Shire that such a request for the monitoring of the active metabolite is consistent with the current FDA guidance on the conduct of bioequivalence studies.

A "controlled correspondence" supporting document is enclosed which provides a justification that monitoring of anagrelide's active metabolite, 3-hydroxy anagrelide, in clinical bioequivalence studies should be considered by the OGD. The document consists of an overview of the contribution of the active metabolite, 3-hydroxy anagrelide to the safety and efficacy of the drug product. The overview is supported by two appendices that provide more detail on the pharmacology, pharmacokinetics and evidence of pre-systemic metabolism of anagrelide.

You will have received a copy of a letter (dated 17 June 2004) sent to Dr. Robert Justice at the Division of Gastroenterology and Coagulation Drug Products that accompanied the recent labelling supplement to the Agrylin NDA. As mentioned earlier, a copy of the NDA supplement is included in this request for your information (pertinent clinical information is provided by the following studies: SPD422-103 renal impairment, SPD422-104 hepatic impairment, SPD422-107 aspirin interaction, SPD422-109 food effect, SPD422-202 clinical paharmacokinetic study in patients).

I look forward to hearing from you in the near future regarding the active metabolite question posed above. If deemed appropriate, Shire would welcome the opportunity to meet with representatives of OGD to further discuss the issues.

Should you have any questions, please do not hesitate to contact me at 240-453-6442 (phone) or 240-453-6456 (fax) or via email at csymington@us.shire.com.

Kind regards,

Catherine N. Symington
Senior Manager, Regulatory Affairs

Enclosures:

1. Supporting Documentation to justify metabolite monitoring
2. 12 March 2004 NDA supplement addressed to Division of Gastroenterology and Coagulation Drug Products (copy of cover letter)
3. 17 June 2004 NDA supplement addressed to Division of Gastroenterology and Coagulation Drug Products (full copy)